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(54) [Title of the Invention]

Drug for Improving the Life Extension Rate of Kidney Patients

(57) [Summary]

[Objective]

To offer the drug for improving the life extension rate of kidney patients.

[Method to Achieve the Objective]

Drug for improving the life extension rate of kidney patients which contains an acrylic

type water absorbent resin as the effective component.

[Scope of the Pat nt Application]

[Claim 1]

Drug for improving the life extension rate of kidney patients characterized by the fact that it contains an acrylic type water absorbable resin as the effective component.

[Claim 2]

Drug for improving the life extension rate of kidney patients in which the effective component is an alkali metal salt type polymer of acrylic acid or methacrylic acid, as was described in Claim 1.

[Claim 3]

Drug for improving the life extension rate of kidney patients in which the effective component is an alkali earth metal salt type polymer of acrylic acid or methacrylic acid, as was described in Claim 1.

[Claim 4]

Drug for improving the life extension rate of kidney patients in which the effective component is a self cross linking type acrylic acid metal salt type polymer, as was described in Claim 1.

[Claim 5]

Drug for improving the life extension rate of kidney patients in which at least a part of the metal salt is a calcium salt, as was described in Claim 4.

[Detailed Explanation of the Invention]

[0001]

[Technical Field in Which this Invention Belongs]

This invention relates to the drug for improving the life extension rate of kidney patients. In particular, it relates to the new drug for improving the life extension rate of kidney patients which is administered orally to the acute and chronic kidney patients who are

receiving the hemodialysis, or to the kidney patients who do not need hemodialysis yet but who's water intake is limited due to the deterioration of their kidney function, and which can extend the life of the said patients.

[0002]

[Existing Technology]

Acrylic type water absorbent resins such as sodium poly acrylate, etc., have been used for the hygiene products such as sanitary napkins, diapers, disposable wipe cloths, etc., and also as the food additives, and farm and garden products. Also it has been known in the references that this can be utilized as the digestive ulcer treatment drug (German Patent No. 2412090), for the bleeding control and as a scratch protecting agent (Patent Kokai No. S62-70318), and as the intoxication prevention agent (Patent Kokai No. H1-153643), etc.

[0003]

On the other hand, concerning the acute and chronic kidney patients who are receiving the hemodialysis, or patients who do not need hemodialysis yet but who's kidney function has deteriorated, the nitrogen, the metabolic waste and water, etc., which should be discharged into the urine in normal cases, will be accumulated in the body. Therefore, the life of kidney patient is said to be quite short compared with that of a normal person.

[0004]

The metabolic waste, water, etc., that is accumulated in the body can be removed by the above mentioned hemodialysis, but this is not sufficient, so that it has been desired to develop the new technology and drugs which can remove the un-necessary material that is accumulated in the patient's body as much as possible to lengthen the life of the patient.

[0005]

[Problem That this Invention Intends to Solve]

Therefore, the objective of this invention is to offer a new oral administered drug which can improve the life extending rate of the kidney patients.

[0006]

The inventors of this invention studied to achieve the above mentioned objective, and as the result, they discovered that some kinds of water absorbent resins that have been used for the hygiene products, etc., have the surprising effect of improving the life extending ratio of the patient when it is administered orally to the patient, although the reason for this is not clear, and also that the oral administration with a dosage that can provide this effect is very safe, so that this invention was completed.

[0007]

[Method to Solve the Problem]

According to this invention, the drug that can improve the life extending ratio of kidney patients which is characterized by including an acrylic type water absorbent resin as the effective component, can be offered.

[0008]

[Form of Enforcing this Invention]

One preferred example that is included in the above mentioned acrylic type water absorbent resins that is the effective component of the drug for improving the life expectancy of kidney patients of this invention, can be selected from the polymers that contain an acrylic type monomer that can be indicated by the general formula,

$CH_2= CR^1 COOR^2$

[in the formula, R^1 indicates a hydrogen atom or a methyl group, and R^2 indicates a hydrogen atom or a metal atom.]

as the essential structural unit, and the cross linked material of the said polymer.

[0009]

Here, the metal which forms the metal salt can be for example, the alkali metals such as sodium, potassium, lithium, etc., and the alkali earth metals such as calcium, magnesium, etc.

[0010]

The above mentioned preferred acrylic type water absorbent polymer includes acrylic acid type polymers, acrylic acid metal salt type polymers, methacrylic acid type polymers and methacrylic acid metal salt type polymers, and each polymer may be the respective cross linked type polymer also. Among these, the cross linked material of poly acrylic acid or poly acrylic acid alkali metal salts are preferred, and further, the one in which a part of the said cross linked material has the form of a calcium salt, is the most suitable.

[0011]

The above mentioned cross linked material includes the self cross linked material which was obtained without using any cross linking agent, and the cross linked material which is obtained by normal methods that use various cross linking agents that are commonly used.

[0012]

Multi- valent allyl compounds, multi- valent vinyl compounds, multi- valent epoxy compounds, halo epoxy compounds, multi- valent alcohols, multi- valent amines, hydroxy vinyl compound, etc., can be used as the cross linking agent. The representative cross linking agents are listed below.

[0013]

Multi- valent allyl compounds : N, – di- allyl acryl amide and N, – di- allyl methacryl amide (from now on, these will be indicated as "N, – di- allyl (meth) acryl amide"), di- allyl amine, di- allyl methacryl amine, di- allyl phthalate, di- allyl maleate, etc.

[0014]

Multi- valent vinyl compounds : Di- vinyl benzene, N, – methylene bis (meth) acryl amide, ethylene glycol di (meth) acrylate and poly ethylene glycol di (meth) acrylate (from now on, these will be indicates as "(poly) ethylene glycol di (meth) acrylate"), poly propylene glycol di (meth) acrylate, tri metharol propane tri acrylate, etc.

[0015]

Multi valent epoxy compounds : (poly) ethylene glycol di- glycidyl ether, (poly) propylene glycol di- glycidyl ether, glycerine -1, 3- di- glycidyl ether, tri methylol propane tri glycidyl ether, (poly) glycerine poly glycidyl ether, etc.

[0016]

Halo epoxy compounds : epi chloro hydrine, α - methyl chloro hydrine, etc.

[0017]

Multi- valent alcohols : (poly) glycerine, (poly) ethylene glycol, tri methylol propane, penta erythritol, etc.

[0018]

Multi- valent amines : ethylene diamine, etc.

[0019]

In addition, the above mentioned acrylic acid type polymers, acrylic acid metal salt type polymers, methacrylic acid type polymers and methacrylic acid metal salt type polymers include not only the homo polymers of acrylic acid and methacrylic acid, but also the co-polymers of these, and the co-polymers of each of these monomers and other monomers that can co-polymerize with these, or the co-polymers with the polymers that can graft polymerize with these too. These co-polymers may be random polymers, block polymers or graft polymers.

[0020]

Here, those that can be listed as other monomers that can co-polymerize with (meth) acrylic acid are for example, alkyl (meth) acrylates such as hydroxy ethyl (meth) acrylate, (methoxy) poly ethylene glycol (meth) acrylate, glycerin (meth) acrylate, glycosyl ethyl (meth) acrylate, etc.; acryl amide type compounds such as N, – di-methyl acryl amide, acryl amide, etc.; carboxylic acid type compounds such as maleic acid and its metal salts, itaconic acid and its metal salts, etc.; sulfonic acid type compounds such as 2- acryl amide -2-methyl propane sulfonic acid and its metal salts, vinyl sulfonic acid and its metal salts, styrene sulfonic acid and its metal salts, etc.; and – vinyl pyrrolidone, etc.

[0021]

Also, those that can be listed as the polymers that can graft polymerize with (meth) acrylic acid are for example, the hydrophillic poly saccharides such as starch, carrageenan, agarose, carboxy methyl cellulose, etc.

[0022]

Some of the above mentioned various water absorbent resins are sold commercially, and they can be produced by ordinary methods too. General production methods that are known are for example, the method in which the monomer is polymerized in an aqueous solution of monomer (aqueous solution polymerization), the method in which the suspension liquid of an aqueous monomer solution is made in a non- aqueous organic solvent, and this is polymerized (reverse phase suspension polymerization), and the method in which the aqueous solution of the polymer is cross linked by using a cross linking agent (polymer cross linking method), etc. The water absorbent resin utilized in this invention can be made by any of these methods.

[0023]

Especially, the self cross linking type acrylic acid alkali metal salt type polymer which is one of the suitable effective components of this invention should be preferably produced by polymerizing (reverse phase suspension polymerization) by suspension - dispersing a high concentration aqueous solution of the acrylic acid alkali metal salt in an organic solvent. (For example, see Patent Kokoku No. S54-30710 Official Gazette)

[0024]

Also, the self cross linked type acrylic acid metal salt type polymer in which a part of alkali metal atoms are substituted by calcium and which is one of the especially suitable effective components in this invention, can be produced for example by suspension - dispersing a high concentration aqueous solution of the acrylic acid alkali metal salt and acrylic acid calcium salt in an organic solvent, or more preferably, by slowly adding an aqueous solution of calcium chloride into the water swelled polymer of the self cross linked type acrylic acid alkali metal salt obtained by the above mentioned method, and by performing the counter ion exchange.

[0025]

Thus, the acrylic type water absorbent resin that can be utilized as the effective component of the drug for improving the life extending rate of kidney patients of this invention can be produced.

[0026]

The acrylic resins that are especially suitable for this invention are for example, the ones of which the physiological saline solution absorbing ability (volume (mL) of a physiological saline solution absorbed per 1 g) is 5 to 100, more preferably 15 to 70.

[0027]

Concerning the administration of the drug for improving the life extending rate of kidney patients of this invention, the acrylic type water absorbent resin that is obtained in the above mentioned manner, is administered orally to the patients who need to absorb-remove the uric acid, water and potassium ions, in an ordinary form that can be obtained, for example, the powder form, a fine powder form, a bead- like form, a flake-like form, the gel form, etc. Also, the same as for ordinary oral administering agents, a general support material can be used to make it into an appropriate shape such as tablets, granules, capsules, etc., to be used.

[0028]

The dosage can be determined at any level depending on the patient to which it is to be administered, and the dosage is not particularly limited, however, generally, the amount of the effective component should be in the range of 5 to 20 g per day.

[0029]

Of course, since we know that the above mentioned effective component itself has

been suggested to be used as the digestive ulcer treating agent or as a bleeding control agent, etc., it does not have toxicity, practically, and it is safe even if it is applied in a living body, and even if it is administered orally as in this invention, it will not be absorbed into the internal body, practically, so that its safety is secured.

[0030]

Thus, if the drug for improving the life extending rate of kidney patients of this invention is utilized, the life of the patient who is receiving the hemodialysis or the life of the patient who does not yet need dialysis but who's kidney function has deteriorated, can be improved.

[0031]

[Actual Examples]

Next, in order to further explain this invention, the methods to produce the water absorbent resin that is utilized as the effective component of this invention will be listed, and then, a prescription example of the drug for improving the life extending rate of kidney patients of this invention, and the test examples that used this drug, will be explained.

[0032]

[Production Example 1]

Production of sodium poly acrylate cross linked material

1600 mL of cyclo hexane and 16.32 g of sorbitan mono stearate were put into a 5000 mL flask with 4 openings equipped with a mixer, a reflux condenser, a dropping funnel and the pipe for introducing nitrogen gas. While blowing the nitrogen gas into the flask to remove the oxygen that was dissolved, the temperature was increased to 75 °C.

[0033]

In a separate flask, 510 g of 80 % acrylic acid was added while cooling from the outside, and 544 g of 30 % aqueous NaOH was added to neutralize it, and then, 1.62 g of potassium per sulfate was dissolved. Thereafter, the nitrogen gas was blown- in to remove the oxygen that was dissolved in the aqueous solution.

[0034]

The contents of flask were dropped into the above mentioned flask with 4 openings over a period of 1 hour, and the polymerization reaction was performed. The cyclo hexane was distilled out under reduced pressure, and the remaining swelled polymer was dried at 80 to 100 °C under reduced pressure. By using 300 mL of cyclo hexane, the cross linked polymer that was recovered was washed twice, and the sorbitan mono stearate was removed.

[0035]

Thus, the polymer of which the physiological saline solution absorbing ability per 1 g of cross linked polymer was 53 g, was obtained.

[0036]

[Production Example 2]

Production of sodium poly acrylate cross linked material

The same as in Production Example 1, two types of polymers of which the physiological saline solution absorbing ability per 1 g of cross linked polymer were each 48 g and 58 g, were obtained. These are called polymer A and polymer B.

[0037]

[Production Example 3]

Production of poly acrylic acid cross linked material

50 g of sodium poly acrylate obtained in Production Example 1, was added into 15 L of an aqueous solution of 77.5 g hydrochloric acid while stirring, and this was left for 2 days, and the sodium ions were replaced by hydrogen ions. The obtained polymer was filtered and recovered, and it was washed with de-ionized water, and thereafter, it was added into 3 L of de- ionized water and it was made into a slurry. The water and hydrochloric acid were distilled out from this slurry, and the dried polymer was obtained.

[0038]

The Na content in the obtained polymer was 530 ppm; 99 % or more of the sodium acrylate in the polymer was converted into acrylic acid. The physiological saline solution absorbing ability of this was 1 g. From now on, this will be called polymer C.

[0039]

[Production Example 4]

Production of calcium poly acrylate cross linked material

100 g of sodium poly acrylate obtained in Production Example 1, was put into 5 L of de-ionized water, and it was swelled. While stirring this, 2.4 L of a 0.2 M aqueous calcium chloride solution was dropped into this, and the desired polymer was obtained.

[0040]

In the said polymer, 90 % or more of the sodium acrylate in the raw material polymer was converted into calcium acrylate. The physiological saline solution absorbing ability of this was 18.5 g. From now on, this will be called polymer D.

[0041]

[Production Example 5]

Production of sodium poly methacrylate cross link d material

The desired polymer was obtained in the same way as in Production Example 1, except that 714 g of 70 % methacrylic acid was used instead of 80 % acrylic acid, and that it was neutralized by 544 g of a 30 % aqueous NaOH solution while cooling, and then, 0.04 g of methylene bis acryl amide (cross linking agent) and 1.63 g of potassium per sulfate were dissolved, and thereafter, nitrogen gas was blown in and the oxygen that was dissolved in the aqueous solution was removed.

[0042]

The physiological saline solution absorbing ability of this material was 47 g.

[0043]

[Production Example 6]

Production of poly methacrylic acid cross linked material

The desired polymer was obtained in the same way as in Production Example 3, except that 55 g of the sodium poly methacrylate cross linked material obtained in Production Example 5 was used instead of the sodium poly acrylate cross linked material.

[0044]

The physiological saline solution absorbing ability of this material was 31 g.

[0045]

[Production Example 7]

Production of calcium poly methacrylate cross linked material

The desired polymer was obtained in the same way as in Production Example 4, except that 110 g of the sodium poly methacrylate cross linked material obtained in Production

Example 5 was used instead of the sodium poly acrylate cross linked material.

[0046]

The physiological saline solution absorbing ability of this material was 20 g.

[0047]

[Production Example 8]

Production of sodium + calcium poly acrylate cross linked material (Na / Ca = 3 / 1)

The desired polymer was obtained in the same way as in Production Example 1, except that it was neutralized by using 408 g of a 30 % aqueous NaOH solution instead of using 544 g of 30 % aqueous NaOH solution, and also that the neutralization was performed by using the suspension liquid which consisted of 126 g of $Ca(OH)_2$ and 150 g of de- ionized water.

[0048]

The calcium substitution degree of this material was 25 %, and the physiological saline solution absorbing ability of this material was 43 g.

[0049]

[Prescription Example 1]

Production of capsule agent

As the effective component, the self cross linked material of sodium poly acrylate obtained in Production Example 1 (neutralization degree : 72 %, water absorbing ability : 53 g, from now on, this will be called polymer A.) was filled into an oral administering gelatin capsule of the desired size, and 1000 hard gelatin capsules which contained 250 mg per capsule, were prepared.

[0050]

[Prescription Example 2]

Production of capsule agent

As the effective component, polymer A and the self cross linked material of calcium poly acrylate obtained in Production Example 4 (neutralization degree : 70 %, water absorbing ability : 18 g, from now on, this will be called polymer B.) were uniformly mixed and it was filled in an oral administering gelatin capsule of the desired size, and 1000 hard gelatin capsules which contained 150 mg of polymer A and 150 mg of polymer B per capsule, were prepared.

[0051]

[Pharmacological Test Example 1]

10 Wister type male rats, 10 weeks old, (a product of Nihon Charles River Co.) were used for 1 group. After they were grouped, the kidneys were totally removed from all the rats on the afternoon of the first day. Namely, the rat was put under anesthesia by Nembutal, and the hair on both the back and sides were shaved, and the abdominal wall was cut open at the lower end of the ribs. The kidneys that were wrapped with fat tissue were pulled out, and the renal artery, the renal vein and the urine tube were tied up, and thereafter, the kidney was cut off, and the incisioned part of the abdominal wall and skin were sutured together.

[0052]

As the drug to be tested, each of the polymers (polymer A ~ D) that were obtained in Production Examples 2 ~ 4, and commercially sold sodium poly acrylate (commercial name of 196- 10765, food additive grade, made by Wako K.K., from now on this will be called polymer E) were suspended in the commercially sold "shiso?" oil, and an administering liquid with a concentration of 250 mg / mL was prepared. The

administered amount at each time was decided to be 1 mL. The administration was done for a total of 5 times at 9 AM from the second day through the fifth day. 15 mL of water and then 1 mL of the suspension liquid of the drug to be tested were orally administered by using a gastric tube (Experiment group).

[0053]

As the control group, a group was provided to which 15 mL of water and 1 mL of only "shiso?" oil which did not contain the drug was administered instead of the suspension liquid of the drug.

[0054]

During the period of the experiments, rats of each group could eat food freely, however, their water intake was only the load given the above mentioned oral administration.

[0055]

The survival ratios of the rats in each group in the above mentioned experiment were obtained, and also the average survival times were measured.

[0056]

The survival time was indicated by (average survival time) ± (standard deviation), and it was examined by using the "log rank? " method.

[0057]

The obtained survival ratios are shown in Figure 1, and the average survival times are shown in Table 1.

[0058]

In the figure, (1) indicates the control group, (2) indicates the group in which polymer A

was administered, (3) indicates the group in which polymer B was administered, (4) indicates the group in which polymer C was administered, (5) indicates the group in which polymer D was administered, and (6) indicates the group in which polymer E was administered. The black triangle marks indicate the times of administering the suspension liquid.

[0059]

[Table 1]

Drug tested	Survival time (Average survival time ± SD)
Nothing (control group)	64.8 ± 8.97
Polymer A	87.4 ± 15.0 *
Polymer B	90.9 ± 11.9 *
Polymer C	78.3 ± 15.8
Polymer D	76.8 ± 17.2
Polymer E	81.6 ± 11.6 *

* indicates $p < 0.01$ to the control group.

[0060]

The following is clear from the above mentioned results.

[0061]

Namely, all groups to which the drug was administered showed increased survival rates and increased average survival times compared with the control group. Especially, the groups in which polymer A, polymer B and polymer E were administered (in the figure these are shown by the lines (2), (3) and (6)), extended their average survival time by about 17 hrs, 23 hrs and 26 hrs compared with the control group, and a significant difference ($p < 0.01$) was recognized. Also, as can be seen in figure, the difference between the groups began to appear around 54 hours after the experiment was started,

and thereafter, the control group rats were all dead within about 78 hours after experiment was started, however, in the group in which polymer D was administered (line (5)), in the group in which polymer C was administered (line (4)), in the group in which polymer E was administered (line (6)), in the group in which polymer A was administered (line (2)), in the group in which polymer B was administered (line (3)), when the test was finished, namely at the time point of 102 hours after the experiment was started, 2 rats, 1 rat, 2 rats, 3 rats, and 2 rats, respectively were still alive.

[0062]

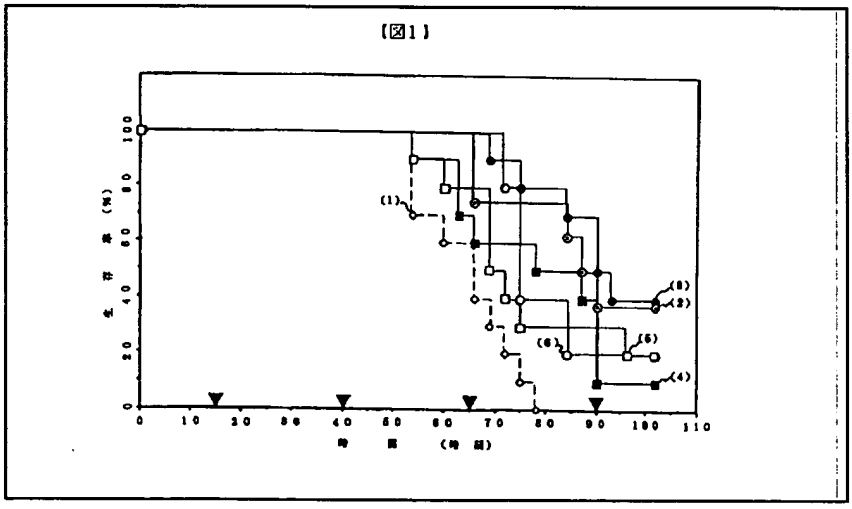
From the above description, it is clear that a life extending effect can be obtained by administering the effective component of this invention.

[Simple Explanation of the Figures]

[Figure 1]

This is the graph which indicates the results of the life extending rate obtained in the pharmacological test example 1.

Figure 1



In the figure the y axis indicates the Survival rate (%), and the x axis indicates Time (hour).

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